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EXAMINER

TUCKER, ZACHARY C

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 09/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/632,531

Applicant(s)

HAYASHI ET AL.

Examiner

Zachary C. Tucker

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Pre. Amdt 26 August 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 15-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 02 January 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>19Aug05, 12Nov04</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Prior to examination, applicants' counsel Marc T. Morley was contacted regarding a Requirement for Restriction in the instant application. The examiner informed Mr. Morley that the Requirement would set forth three Groups as follows:

- I. Claims 15-25, drawn to chemical compounds.
- II. Claims 1-14, drawn to methods of synthesizing the compounds in Group I.
- III. Claims 26-40, drawn to a pharmaceutical composition and methods of treatment and/or prevention of various disease states, comprising (administering) the compounds of Group I.

Applicants' counsel has elected to pursue the claims drawn to compounds, as were set forth in Group I and Preliminary Amendment was filed wherein all claims except those drawn to compounds have been cancelled. So, the Requirement for Restriction which was communicated to applicants' is rendered moot by the filing of the Preliminary Amendment of 26 August 2005.

There is no Requirement for Restriction, as only one invention, chemical compounds, is presently claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Art Unit: 1624

Claims 15-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Indefinite claim language is recited in the independent claim, 15, and since all claims (save 21) depend directly from that claim, all claims are indefinite.

Claim 15 is indefinite in scope by virtue of the many recitations of "optionally substituted," which modify aryl, amino, heteroaryl, phenyl and nitro groups, in substituents R₁, R₁', R₁", R₂, R₃, R₄, R₅ and R₆. When read in light of the specification, these terms are not clear and well-defined. Pages 18 and 19 of the written description state that "substituted" has its "ordinary meaning, such as" and a list of exemplary substituents is provided. Chemists of ordinary skill will differ in opinion as to what constitutes an "ordinary" substituent. Even if the list of exemplary substituents which is provided in the specification is considered as a claim limitation, the language "such as," which prefaces that list, renders the scope of the definition provided unclear. "Preferably" is also employed in the definitions of these terms in the specification (see for example page 19, line three).

In the sentence bridging pages 18 and 19, the instant specification states that "substituted is also as broad as the definition provided in US Patent No. 6,509,331," but there is no specific definition of "substituted" in that patent. Various definitions of different substituted groups are provided, but no single definition for "substituted" in general. Additionally, in lines 3-14 of page 19 of the instant specification, the substituents that applicants intend for the term "substituted" to stand for include several

Art Unit: 1624

"substituted" groups. So, when considered in light of this definition, substituted is defined in terms of other "substituted" functional groups, further confounding any effort to determine exactly what applicants intend for the term to describe.

Exactly what applicants intend for each of the recitations of "substituted" in reference to aryl, amino, heteroaryl, phenyl and nitro groups to embrace therefore is not known.

This indefiniteness rejection will be overcome by an amendment that limits the optionally substituents to a specific group ("selected from the group consisting of"), along the lines of –

alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminoacyl, aminoacyloxy, oxyacylamino, cyano, halogen, hydroxyl, carboxyl, carboxyalkyl, aryl, aryloxy, heteroaryl, heteroaryloxy, hydroxyamino, alkoxyamino, nitro, --SO-alkyl, --SO-aryl, --SO-heteroaryl, --SO₂-alkyl, SO₂-aryl and --SO₂-heteroaryl.

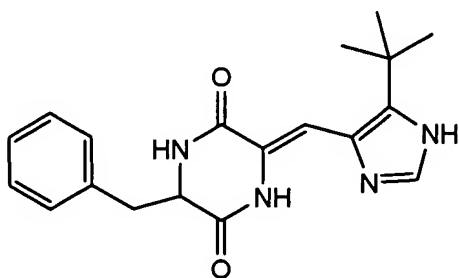
These terms are found in lines 3-14 of page 19 of the specification.

Claim 15 is further indefinite because the proviso at the end of that claim contradicts itself. The proviso specifies that when R₁, R₁', R₂, R₃, R₄ and R₅ are each a hydrogen atom, that X₁ and X₂ are not oxygen, and also that R₄ is neither 3,3-dimethylpropyl-1-ene nor *hydrogen*. So, R₄ cannot at once be a hydrogen atom and also not be a hydrogen atom. The proviso in claim 15 has been interpreted as though "or a hydrogen atom" were not recited in condition "2)."

Claim 19, in addition to being indefinite for depending from an indefinite base claim, is indefinite because the recitation "wherein the saturated C₁-C₁₂ alkyl is a tertiary butyl group," does not make clear which saturated alkyl group is being further limited. There are several recitations of "saturated alkyl" in claim 15.

Art Unit: 1624

Claim 25, in addition to being indefinite for depending from an indefinite base claim, is indefinite because the compounds "KPU-11" and "KPU-66" are not defined in the specification, as opposed to the other "KPU" compounds recited. If the examiner is incorrect in this observation, applicants should point to where the structures of "KPU-11" and "KPU-66" are shown in the specification. In addition, the compound, *t*-butyl-phenylahistin, specified in claim 25, although it is of known structure –



lacks antecedent basis in claim 15, because

only *dehydro*phenylahistin compounds are embraced by formula (I). *t*-Butyl-phenylahistin is not a *dehydro*phenylahistin compound; the phenyl ring is bonded to the 2,5-diketopiperazine core via a saturated methylene group.

Amendment of claim 25 to specify *t*-butyl-*dehydro*phenylahistin, and deletion of "KPU-11" and "KPU-66," or indication of where in the specification those two compounds are defined would overcome this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

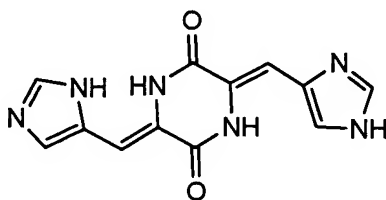
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Art Unit: 1624

Claims 15-17, 19 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Augustin, M. "Die Umsetzung des 2,5-Diketopiperazins mit Aldehyden und Nitrosoverbindungen" *Journal für Praktische Chemie*, vol. 32(4), pages 158-166 (1966).

A compound according to instant claims 15-17, 19 and 22 is disclosed on page 161 of Augustin, named, 3,6-Bis[imidazoliden-4(5)]-2,5-diketopiperazin or in English, 3,6-bis-(imidazole-4-ylmethylene)-2,5-diketopiperazine. The compound has the structure depicted here:



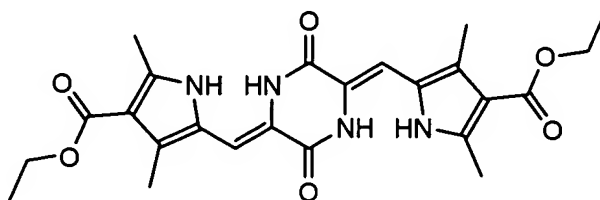
and is embraced by instant claims 15-17, 19 and 22 wherein $n=0$; Z_3 and Z_1 are nitrogen atoms, Z_2 and Z_4 are carbon atoms and two of the dashed lines are double bonds, the other two are single bonds R_1 , R_1' , R_1'' , R_2 , R_3 , R_4 , R_6 are hydrogen; X_1 and X_2 are oxygen; Y is a nitrogen atom. Claim 19 is included in this rejection because it further modifies an optional element of claim 15, the saturated alkyl group, which is not required in claim 15 compounds.

The proviso in claim 15, as it has been interpreted in the preparation of this Office action, does not apply to this compound.

Art Unit: 1624

Claims 15, 17, 18, 19 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Küster and Köppenhofer, "Über einige Pyrrolderivate" *Z. Physiol. Chem.*, vol. 172, pages 126-137 (1927).

A compound according to instant claims 15, 17, 18, 19 and 22 is disclosed in Küster and Köppenhofer at lines 3-4, named 2,2-di-(3,5-dimethyl-4-carboxäthylpyrral-)methyl-2,5-diketopiperazin, designated "(I)." The compound is alternatively named 3,6-bis-[(4-carboxy-3,5-dimethyl-2-pyrrolyl)methylene]-2,5-piperazinedione diethyl ester, by contemporary nomenclature. The structure is as shown here –



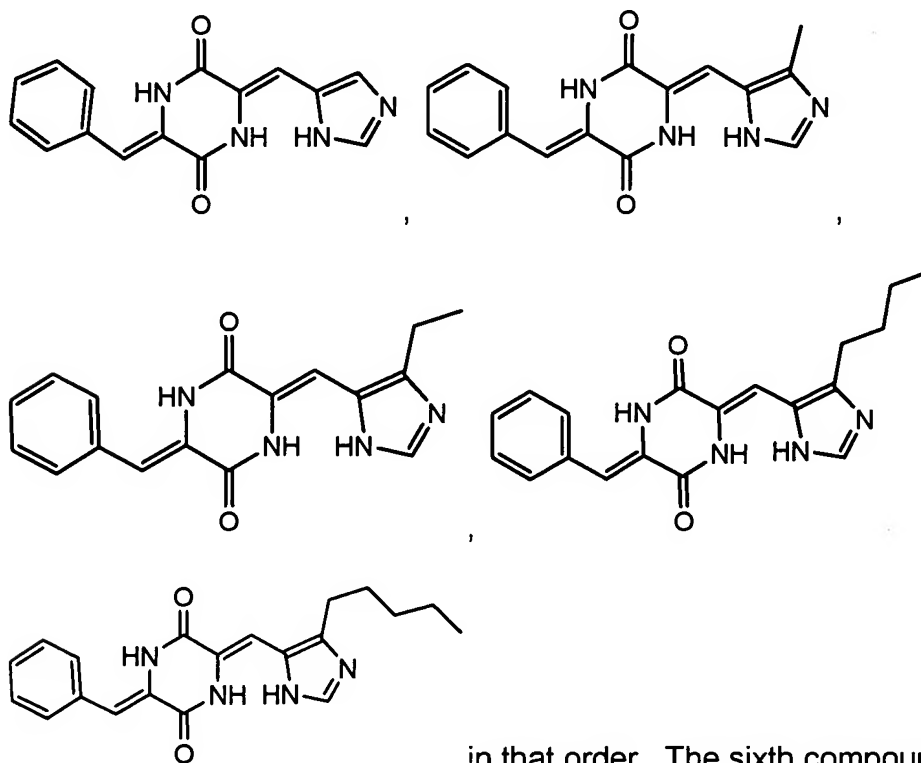
which is a compound according to claims 15, 17, 19 and 22 wherein $n=0$, Z_4 is a nitrogen atom, Z_1 , Z_2 and Z_3 are carbon atoms and two of the dashed lines are double bonds, the other two are single bonds; R_1 , R_1' , R_4 and R_5 are all methyl, R_1'' is $-\text{CO}-\text{O}-R_7$ where R_7 is ethyl; X_1 and X_2 are both oxygen; Y is methylene group substituted with one R_5 , where R_5 is acyl. Ethoxycarbonyl is an acyl group of a carbonic acid half-ester, and is within the broadest reasonable interpretation of "acyl."

Claim 19 is included in this rejection because it further modifies an optional element of claim 15, the saturated alkyl group, which is not required in R_2 and R_3 of claim 15 compounds when, for example, R_2 or R_3 are other than saturated alkyl, as is the case in the reference compound.

Art Unit: 1624

Claims 15-17, 18, 19, 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Canadian Patent Application CA 2 403 790 (Kanzaki et al).

Compounds according to claims 15-17, 19 and 22-24 are disclosed on page 13, lines 10-14. These five compounds have the structures depicted below –



in that order. The sixth compound named on page 13 of Kanzaki et al is excluded by the proviso at the end of instant claim 15.

The above-depicted molecular structures are embraced by instant claims 15-17, 19 and 22-24 where $n=1$, Z, Z₁, Z₂, Z₃ and Z₄ are carbon atoms, forming a phenyl ring; R₁, R₁' and R₁'', R₂, R₃ and R₆ are each hydrogen; R₄ is either hydrogen or methyl, ethyl, butyl or pentyl (saturated alkyl); X₁ and X₂ are oxygen; Y is a nitrogen atom. The case where R₄ is hydrogen is not excluded by the proviso of instant claim 15 because, as explained above in the rejection of that claim under 35 U.S.C. 112, second

Art Unit: 1624

paragraph, R₄ cannot at the same time both be hydrogen and not be hydrogen, as is required by language of the proviso.

Claim 19 is included in this rejection because it further modifies optional elements of claim 15, which are not required to be unsaturated alkyl in the above-depicted compounds from Kanzaki et al, for example R₂, R₃ are permitted to be saturated alkyl groups, but in Kanzaki et al's compounds, hydrogen atoms are at those positions on the molecule.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 19 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over CA 2 403 790 (Kanzaki et al).

Kanzaki et al is applied against claims 19 and 25 as set forth above in the rejection of claims 15-17, 18, 19, 22-24 under 35 U.S.C. 102(b).

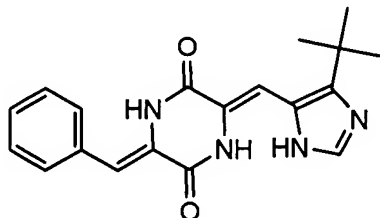
The deficiency of Kanzaki et al with respect to instant claim 19 is that Kanzaki et al does not disclose the synthesis of a compound wherein the R₇ position (corresponding to R₄ of claim 15) is a *t*-butyl group. In Kanzaki et al's preferred embodiment, however, R⁷ is alkyl. One of the expressly suggested saturated alkyl groups for R₇ (see page 9, lines 7-14) is *tert*-butyl. Thus, one of ordinary skill in the art

Art Unit: 1624

would have found it obvious to make a compound according to Kanzaki et al wherein the R₇ group was *tert*-butyl.

A chemist of ordinary skill in the art understands the teachings in a patent publication like Kanzaki et al to be particularly applicable to the preferred embodiments, that is, to the compounds which were actually made by the inventors in the reduction to practice of the invention disclosed in such a publication. In the case of Kanzaki et al, the compounds named on page 13 of the publication include R₇ alkyl substituted compounds. For one of ordinary skill to replace the *n*-butyl R₇ group with a *tert*-butyl R₇ group would be obvious, and the motivation to do so would be to provide inhibitors of cell division as is taught on page 5 and pages 34-35 of Kanzaki et al.

A compound according to Kanzaki et al, wherein the R₇ is *tert*-butyl has this structure –



and is dubbed “KPU-2” by applicants. The compound’s structure is shown on page 98 of the specification, recited in claim 25. Compound KPU-2 is obvious over Kanzaki et al.

Drawings

The set of drawings submitted 2 January 2004 are approved. The drawings submitted 1 August 2003, at the time of filing of this application, are not acceptable because they are of poor quality and the characters in many of the figures are too small.

Comment

The terms "substituted alkoxy," "substituted cycloalkyl," "substituted cycloalkenyl," "substituted amino," "--SO-substituted alkyl," "--SO₂-substituted alkyl," though they are named in lines 3-14 of page 19 of the specification, have been left out of the language suggested for overcoming the indefiniteness rejection, for the reasons explained *supra*. The terms "keto," and "thioketo," also named at page 19, are also not included in the suggested language because those groups are divalent, so a recitation of "keto" or "thioketo" would provide for a dangling valency when it is specified as a substituent on a molecule. "Thioalkoxy," also listed in lines 3-14 of page 19 of the specification is not included in the suggested language because the meaning of that term is not understood. The thio- analog of an alkoxy group is "*alkylthio*," not "thioalkoxy." Finally, the term "heterocyclic," although it is named at page 19 of the specification, has not been included in the suggested language because, as opposed to heteroaryl, it is much broader in its scope. Its recitation as an optional substituent provides for compounds which are not possible to make by the methods taught in the specification. An issue under the first paragraph of 35 U.S.C. 112 would be raised should an amendment introducing "heterocyclic" as an optional substituent be submitted.

For example, lactonyl groups, cyclic carbonates, cyclic peroxides, cyclic trioxolanes (ozonides), trioxanes and 1,2-dithianes are all saturated heterocyclic substituents which are very labile; compounds comprising these substituents would not be producible by the exemplified syntheses because the strong alkali employed in the Claisen-Schmidt condensation reaction taught as the first step necessary to make the

Art Unit: 1624

compounds of the invention (Example 1, step "A") would cause those rings to open.

Recitations in formula (I) of "heterocyclic" as a substituent is so broad so as to include a host of compounds which would necessarily have to be made by methods *other than* those which are taught in the specification.

Allowable Subject Matter/Close Prior art

Claim 25 would be allowable if rewritten to overcome the rejections under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Compounds KPU-35, KPU-80, KPU-81, KPU-90 named in claim 25, whose structures are defined in the specification (pages 90 and 100), are novel and unobvious over the prior art, specifically because of the *t*-butyl group on the imidazole ring, which is not specifically disclosed in Kanzaki et al (although it suggested) in combination with specific substituents on the phenyl ring (where Kanzaki et al only discloses compounds with no substituent on the phenyl ring). It cannot fairly be characterized as obvious for one of ordinary skill to select two independent substituents, one on the imidazole ring of Kanzaki et al's compounds, and then also select one substituent on the phenyl ring of those compounds, to arrive at the invention of compounds KPU-35, KPU-80, KPU-81, KPU-90.

Close prior art comes from US 5,852,018 (Bryans et al), which discloses compounds similar to the compounds according to the invention, but Bryans et al's compounds bear two phenyl rings instead of one phenyl ring and one nitrogen-containing five-membered heteroaryl.

Art Unit: 1624

US 6,713, 480 (Fukumoto et al), which is prior art under 35 U.S.C. 102(e), discloses phenylahistin compounds similar to the compounds according to the invention, but Fukumoto et al's compounds are not *dehydrophenylahistins*. The phenyl ring is bonded to the diketopiperazine ring via a saturated methylene group.

Niemann et al, "The Synthesis of the Three Isomeric *dl*- β -Pyridylalanines" *Journal of the American Chemical Society*, vol. 64(7), pages 1678-1682 (1942) also discloses compounds like those which are claimed, but wherein the five-membered nitrogen containing heteroaryl ring is replaced by a pyridine ring. The structure is drawn in the margin of page 1681, in the copy supplied with this Office action.

Like the Niemann et al reference, Yokio et al, "Neihumicin, A New Cytotoxic Antibiotic From *Micromonospora Neihuensis*" *The Journal of Antibiotics*, vol. 41(4), pages 494-501 (April 1988) discloses diketopiperazines which lack the five-membered nitrogen containing heteroaryl ring of the claimed compounds.

Goldfarb et al, "Synthesis of β -2-thienylalanine" *Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya*, pages 98-100 (1958), as abstracted by CAPLUS, discloses a di-2-thienyl-substituted 2,5-diketopiperazine. The structure is depicted in the abstract supplied with this Office action.

Lastly, Asahina, T. *Bulletin of the Chemical Society of Japan*, vol. 5, pages 354-365 (1930) discloses a compound analogous to the one in the Goldfarb et al abstract, except the thienyl rings are replaced by furyl rings.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 8:00am to 4:30pm or Monday from 6:00am to 1:30pm. If

Application/Control Number: 10/632,531

Page 14

Art Unit: 1624

Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

zt

A handwritten signature in black ink, appearing to be "Zt" followed by a stylized flourish.